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To date, breast MRI screening studies have been performed in 165 women. These examination prompted breast biopsy in 15 women, 4 of which yielded malignancy. Results to date demonstrate the feasibility of using breast MRI to screen high risk women. In particular, adherence to strict architectural interpretation criteria has minimized false positive findings. Additional data is required before any statements of the potential efficacy of MRI can be made. This work has been critical to the development of a multi-center pilot trial of breast MRI screening in high risk populations.

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Annual Report for Contract Number DAMD17-96-C-6059

Introduction

The incidence of breast cancer has been increasing. The National Cancer Institute estimates that approximately 1 in 9 women in the U. S. will have breast cancer in her lifetime. This translates into 180,000 American women developing breast cancer each year. This will result in approximately 45,000 deaths due to the disease.(1) As a result of public awareness of the increasing incidence of breast cancer in Western women, combined with media coverage of recent advances in the genetics of breast cancer, women are increasingly concerned about their individual risk of developing breast cancer. Multiple risk factors for the development of breast cancer have been reported. These include family history and obstetrical history.

An analysis of 22 pedigrees with a dominant inheritance pattern for female breast cancer and at least one case of male breast cancer provides strong evidence against linkage to BRCA1 in these families, with a LOD score of -16.63 (odds less than 1 in 10-16.(2) These results indicated that there is a gene or genes other than BRCA1 which predisposes women to early onset breast cancer and which confers an increased risk of male breast cancer, now confirmed with the finding of BRCA2 on chromosome 13.(3) It is likely that other genes that are linked to breast cancer will also be discovered. It is estimated that between 5 and 10 % of all breast cancer is hereditary.

MRI represents an alternative approach to breast imaging. It has the advantage of high soft tissue contrast that can demonstrate breast cancers in radio-dense breasts. This project is aimed at investigating the feasibility of applying contrast enhanced MRI to screen women at high risk for breast cancer. It is hoped that the results of this pilot screening study will provide important information needed to plan a larger clinical trial of screening breast MRI.

Body

Methods

Patients of all races and ethnic backgrounds older than 18 years of age that presented with a documented high risk for breast cancer were considered eligible for this study. As described in our previous report, we have adopted a risk entrance criteria of a 30% lifetime risk of cancer based on the Gail or Claus models. or greater for entrance. Patients who have already had breast cancer would be considered eligible for screening of their contra-lateral breast if their probability of carrying a breast cancer susceptibility gene was greater than 50% based on the Couch model. Patients that have had breast cancer treated over 5 years prior to study entry are considered breast cancer survivors and are eligible.

A detailed clinical history and family pedigree with respect to breast cancer were obtained from each patient.

All patients undergo a physical examination at the Cancer Risk Evaluation Center. In addition, as part of their normal clinical care, all patients have a routine mammogram.

Under this protocol patients undergo yearly MRI examinations performed on a 1.5 Tesla Signa Horizon Echo Speed (General Electric Medical Systems: Milwaukee, WI). The MR examination consist of an axial localizing scan followed by a slab interleaved 3D gradient echo T1 weighted imaging sequence before and after the administration of 20 cc of intravenous gadolinium chelate. An eight-coil bilateral bi-planar array coil is utilized for this study. Fat suppressed images are obtained over an 18 cm field of view using a 512 x 256 matrix and 2-3 mm slice thickness for each breast. The entire acquisition time for both breasts is approximately three minutes. Two sequential acquisitions are obtained after the administration of contrast material.

The high resolution MR images are interpreted as showing suspicious contrast enhancement, probably benign contrast enhancement, or no suspicious findings. Patients with probably benign contrast enhancement were followed at six months and then one year to ensure stability. Suspicious enhancement is defined as : 1. ductal enhancement, 2. Segmental or clumped regional enhancement, or focal mass lesions greater than 5 mm without associated benign features (smooth margins, lobulated margins with internal septations).

Patients with suspicious contrast enhancement underwent short term follow-up exam to ensure the lesion continues to enhance and continues to appear suspicious. During the time of that exam if the lesion continued to appear suspicious it was biopsied.

Results

Technical Objective #1: Estimate the diagnostic yield and positive predictive value of breast MRI for the detection of cancer in a high risk population:

A total of 165 high risk patients were studied. 43 patients underwent 2 yearly screening examinations and 15 patients underwent 3 yearly screening examinations. Thirteen patients presented with associated clinical findings (breast pain, nipple discharge, vague palpable lesions).

One hundred and thirty eight of the MRI examinations were read as normal or containing benign findings. Of the remaining 27, 12 were interpreted as probably benign requiring interval follow-up and 15 were interpreted as suspicious.

Follow-up scans on the probably benign patients did not reveal a change in any cases and not further imaging was performed.

Biopsy was performed in 15 of the cases reported as suspicious (the remaining suspicious findings disappeared on short term follow-up). In 4 cases an invasive malignancy was found. In the remaining cases pathology revealed a benign finding.

The overall yield for the initial breast MRI screen in this patient cohort to date is 4/165=2.4%. The positive predictive value for a suspicious finding to date is 4/15=26%

Technical Objective #2: Compare the diagnostic yield and positive predictive value of mammography and clinical examination:

The patient population studied under this protocol is a heavily prescreened population and therefore patients with suspicious mammogram abnormalities were generally treated for those findings and not entered into this study. The effective yield of mammography in this population was zero. A formal comparison study in a more general population needs to be performed.

Technical Objective #3: Estimate the incidence of detecting interval breast cancers by MRI:

Forty-three women underwent a second yearly follow-up MRI scan, while 15 women underwent 2 follow up MRI scans. No interval cancers were detected.

Technical Objective #4: Determine the interval change in lesions that do not meet the biopsy threshold.

Follow-up scans were obtained on 43 women as described above. No analysis has been performed to date with respect to objective 4. We anticipate this analysis to be completed this year.

Key Research Accomplishment:

Established protocol for screening high risk patients with MRI. This protocol has been used as the template for other high risk screening trials including a multicenter pilot trial Funded by the National Cancer Institute (UO1-CA74680: Protocol 6884), a trial funded by the National Research Counsel in the United Kingdom and a trial organized by the University of Toronto. These groups have collaborated closely under the umbrella of the International working group in breast MRI to organize an international

database to collect data from screening trials around the world in an effort to accelerate our the process of evaluating MRI as a high risk screening examination.

Reportable Outcomes:

1. Database of MRI screening examinations on 165 patients to date.

2. Multicenter High Risk screening pilot study funded by NCI (UO1-CA74680, protocol 6884)

3. Important component toward developing an international MRI screening database.

Conclusion

We have successfully performed an MR screening study on 165 patients at high risk for breast cancer. Abnormal findings prompted a total of 11 biopsies, 4 of which yielded malignant findings.

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Abstract

To date, breast MRI screening studies have been performed in 165 women. These examination prompted breast biopsy in 15 women, 4 of which yielded malignancy. Results to date demonstrate the feasibility of using breast MRI to screen high risk women. In particular, adherence to strict architectural interpretation criteria has minimized false positive findings. Additional data is required before any statements of the potential efficacy of MRI can be made. This work has been critical to the development of a multi-center pilot trial of breast MRI screening in high risk populations.